

From Batch to Flow Processing: Racemization of *N*-Acetylamino Acids under Microwave Heating

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Abstract:

The racemization of *N*-acetylindoline-2-carboxylic acid in *p*-xylene revealed beneficial rate enhancements due to microwave effects, by comparing conventional and microwave heating. The magnitude of this effect was governed by the degree of heterogeneity of the reaction system. The amount of catalyst, the temperature and the amount of cosolvent played a decisive role. The microwave effect completely vanished when a homogeneous solution was heated. During the microwave-assisted heterogeneous racemization of *N*-acetylphenylalanine in *p*-xylene a comparable microwave effect was observed. The microwave effects could be rationalized by adapting selective heating in the phase boundary region of solid and liquid. Additionally, a straightforward translation was achieved from batchwise operation in a stirred reactor to a batch-loop reactor. The (heterogeneous) racemization of *N*-acetylindoline-2-carboxylic acid retained its microwave effect in the loop reactor. Our results demonstrated that avoiding plugging of the tubular reactor is a severe challenge in scaling up.

Introduction

Chiral compounds are ubiquitous in our lives. They are the active constituents of many pharmaceuticals, nutrition products, flavors and fragrances. The essential components are constructed from chiral building blocks and their synthesis becomes more complex in the presence of more stereocenters in their backbone. One route towards enantiomerically pure products involves classical resolution (see Scheme 1).¹ Racemization as part of either a dynamic or a classical resolution process can make the difference between 50% and complete conversion of the substrate.

The relevance of microwave heating in organic synthesis is intensively studied in a small-scale research environment.² There is increasing interest in the scaling-up potential of microwave heating.^{2,3} Because operation in a stirred tank is limited by the penetration depth of microwaves, the best opportunities for the fine chemical industry are considered to lie in a continuous

operation. A continuously operated tubular reactor seems to be promising for application of microwave technology.

In our study, we have selected the racemization of *N*-acetylindoline-2-carboxylic acid to investigate the benefit of microwave heating compared to conventional heating in fine chemical production. In previous studies,⁴ a decreasing heterogeneity of the reaction mixture has demonstrated a diminishing difference between the reaction rates observed for microwave and conventional heating. This effect is referred to as a vanishing microwave effect. In addition to the racemization process in a stirred batch reactor, *N*-acetylindoline-2-carboxylic acid has been racemized in a microwave-heated batch-loop reactor to address the scaling-up potential of microwave heating.

Racemization of *N*-Acetylindoline-2-carboxylic Acid in a Stirred Batch Reactor

In the case of a classical resolution of unnatural *N*-acetylindoline-2-carboxylic acid, the waste stream is enriched in the undesired enantiomer (Scheme 1).⁵ After a separate racemization step, the product/substrate is reintroduced to the process. On the one hand a fast racemization step is preferred, and on the other hand, an easy workup. A cosolvent or a good solvent increases the solubility of the substrate, thus beneficially contributing to the reaction rate of the racemization. However, removal of the solvent (*e.g.*, by distillation) is inefficient from both time and energy perspectives.

For this process, *p*-xylene is selected in view of its high boiling point, inertness, and poorly solubilizing power at room temperature. Indirectly the high boiling point partially compensates for the poor solubility. The product, in the case where *p*-xylene is the solvent, is isolated by an energy-efficient filtration. The actual racemization is catalyzed by acetic anhydride (see Scheme 2).⁶

Acetic anhydride reacts with the acid functionality, thus forming a mixed anhydride. Ring closure eliminates acetate and

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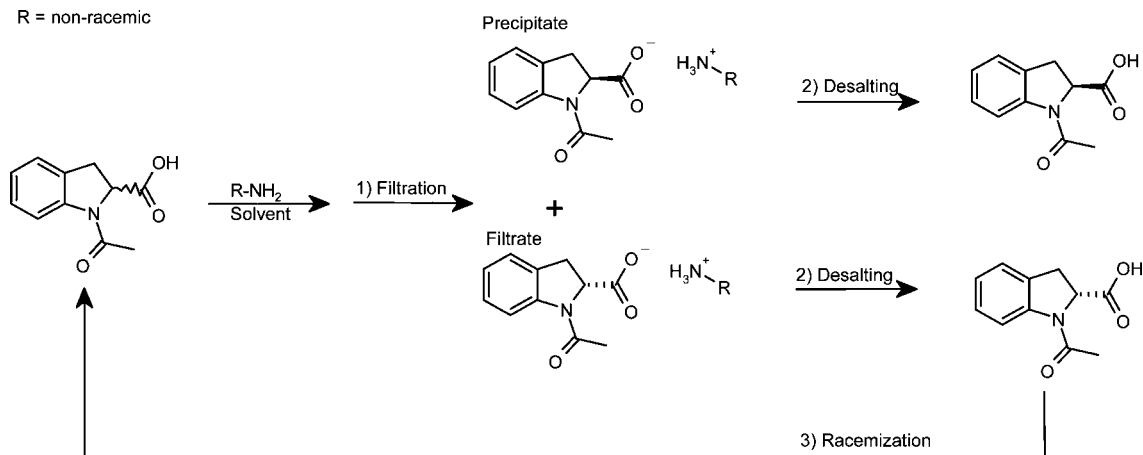
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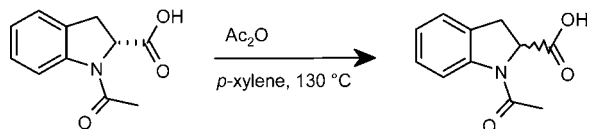
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Scheme 1. Overview of a classical resolution of *N*-acetylindoline-2-carboxylic acid with a non-racemic amine^a

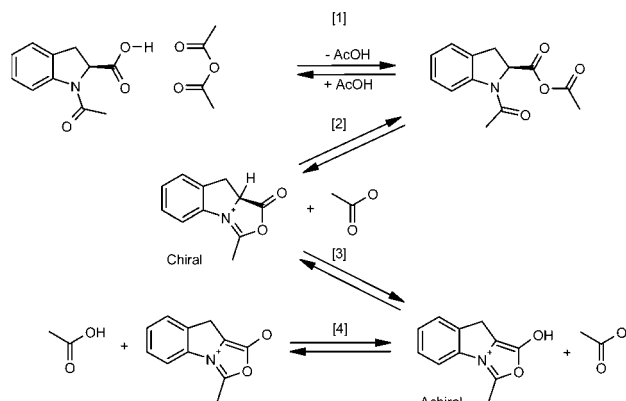


^a The desired diastereomer as precipitate is collected after filtration and desalted to obtain an important intermediate (*S*-enantiomer) in the synthesis of perindopril.¹ The undesired diastereomer as a majority in the filtrate is desalted likewise and is racemized before recycling to the resolution procedure.

Scheme 2. Racemization of (*R*)-*N*-acetylindoline-2-carboxylic acid



Scheme 3. Proposed mechanism of the racemization of (*R*)-*N*-acetylindoline-2-carboxylic acid: [1] formation of asymmetric anhydride, [2] ring closure, [3] keto-enol tautomerization and [4] proton-shift^a



^a After tautomerization the oxazolium is achiral; the reverse reaction can form either enantiomer (*R* or *S*). Only one enantiomer is depicted to make this scheme comprehensible.

gives rise to an oxazolium intermediate. At this stage, the chiral information is lost by keto–enol tautomerization, and due to the reversible character of this reaction, the substrate racemizes completely; see Scheme 3. Other options, such as Pd-catalyzed racemization of amino-acids⁵ and more general racemizations, are reviewed by Zwanenburg et al.⁸

The Influence of Cosolvent. The racemization of *N*-acetylindoline-2-carboxylic acid using acetic acid as a solvent has been reported.⁹ In our case, acetic acid was added to *p*-xylene as a cosolvent to study the role of heterogeneity in correlation with an observed microwave effect for the racemization.⁴ With

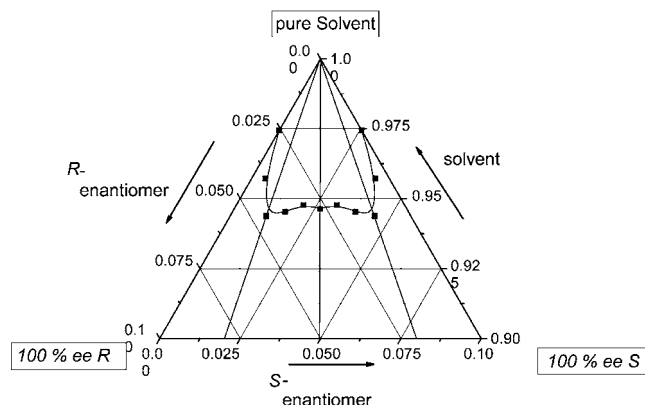


Figure 1. Ternary diagram of (*R*)- and (*S*)-*N*-acetylindoline-2-carboxylic acid and *p*-xylene at 130 °C.

approximately 20 wt % of acetic acid, the reaction mixture becomes homogeneous, and this leads to a complete vanishing of the microwave effect. Figure 1 shows a ternary phase diagram of (*R*)- and (*S*)-*N*-acetylindoline-2-carboxylic acid and *p*-xylene at 130 °C.

The previously mentioned microwave effect is defined as a significant difference between the reaction rates of conventional and microwave heating that cannot be reproduced in a conventional way. The ratio of initial reaction rates (r_{ini}) of both heating techniques enables us to quantify the microwave effect (f_{MW}), see eq 1.

$$f_{\text{MW}} = \frac{r_{\text{ini;MW}}}{r_{\text{ini;CH}}} \quad (1)$$

The Influence of the Amount of Acetic Anhydride. Initial experiments were performed using a scalemic mixture with an enantiomeric excess (ee) of 67% (*R*). Additional experimentation was performed with the (*S*)-enantiomer (99% ee). This study surprisingly revealed a complex pattern that required more detailed investigation. Upon addition of the catalyst, the ee

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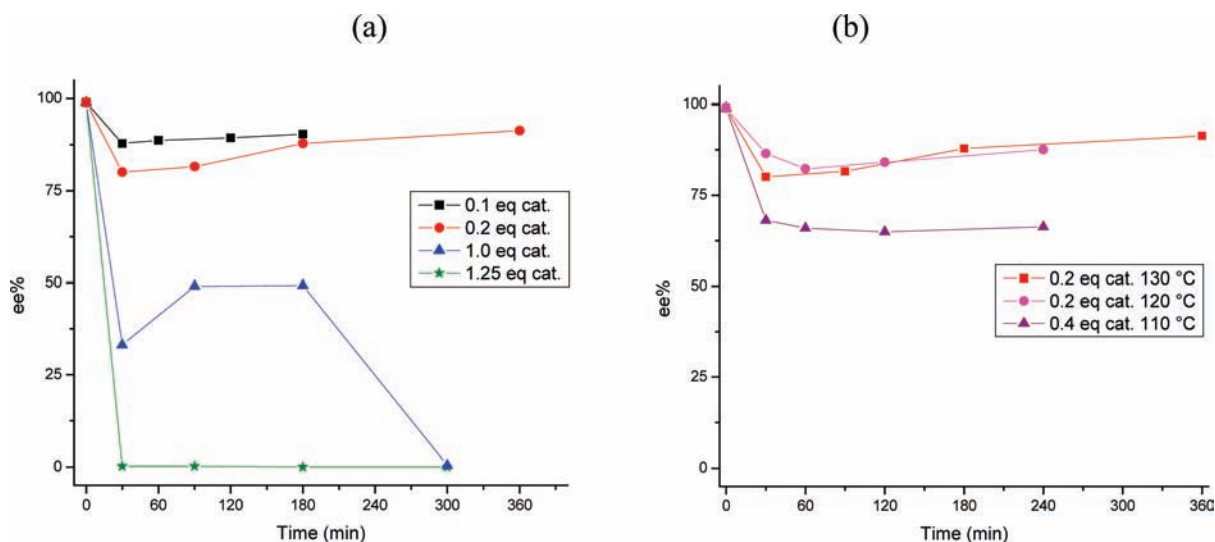


Figure 2. Racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid at 130 °C under conventional heating (a) with various amounts of catalytic acetic anhydride and (b) at different temperatures.

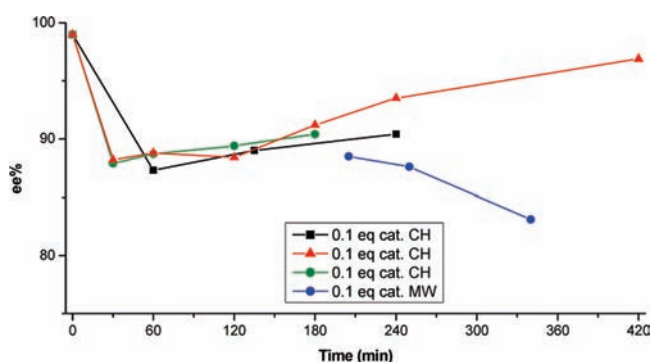


Figure 3. Racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid at 130 °C under conventional heating with 0.1 equiv of catalyst (green line); duplicate (red line) and an extra-dried batch (black line). After 3 h the reaction vessel was transferred to continue the reaction in the microwave oven (blue line).

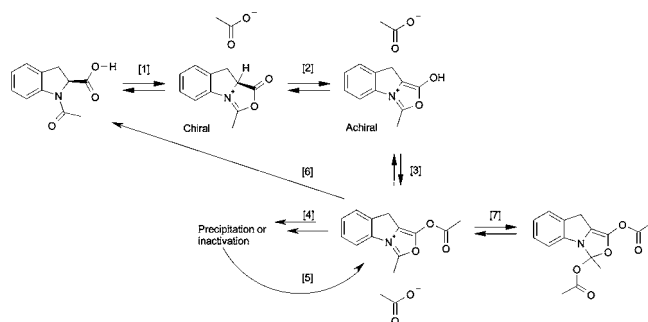
initially decreases as expected, but after a certain period of time the ee levels off under conventional heating. The progress of the racemization depends both on temperature and on the amount of acetic anhydride.

Water may influence the course of the reaction. Related to acetic anhydride, an equimolar amount of water consumes the catalyst and interrupts the racemization process. An amount smaller than one equivalent of water doubles the amount of acetic acid, which acts as a cosolvent that improves the racemization.

Figure 2a shows that the racemization seems to be stopped when using smaller amounts of acetic anhydride. Duplicates illustrate the same behavior. However, to our surprise, when the same reaction mixture was transferred from the oil bath to the microwave oven, the racemization started up again (see Figure 3).

This observation suggests that the molecular species that stops the racemization under conventional heating is actually an intermediate in the process. This intermediate, which has temporarily consumed all of the acetic anhydride, is (partly) dissolved or reactivated by microwave heating. Given the relationship between the enantiomeric excess (e.g., 50%) at the plateau and the amount of acetic anhydride (e.g., 1 equiv) the

Scheme 4. Inhibition of racemization: [1] formation of oxazolium intermediate with acetic anhydride, [2] keto–enol tautomerization, [3] formation of oxazolium acetate with acetic anhydride, [4] precipitation of intermediate, [5] resolving the intermediate by e.g. microwave heating and [6] addition of water regenerates the substrate, [7] acetate bonds to the intermediate (covalent or ionic)^a



^a After tautomerization the oxazolium is achiral; the reverse reaction can form either enantiomer (*R* or *S*). Only one enantiomer is depicted to make this scheme comprehensible.

intermediate presumably originates from a (potentially racemized) substrate and two acetic anhydrides (Figure 2a). One anhydride is used to form the oxazolium intermediate in the first part, and another anhydride may be used to form an eventually inactive structure that inhibits the overall process of racemization (Scheme 4).

Only an increase in temperature or a larger amount of cosolvent can shift the equilibrium to allow completion of the racemization. The solubility does not play a role at lower ee due to the higher solubility of the racemate (see Figure 1).

Shortly after addition of acetic anhydride the solubility of *N*-acetylindoline-2-carboxylic acid temporarily increases. Thereafter, two processes of precipitation and simultaneous racemization allow the ee to slightly increase with respect to the plateau level. The (*S*)-enantiomer selectively precipitates in favor of the (*R*)-enantiomer, due to the presence of a majority of (*S*)-enantiomer crystals. After workup with water the insoluble structure is dissociated into (*R*)- or (*S*)-*N*-acetylindoline-2-carboxylic acid. By applying solid-state NMR the intermediate

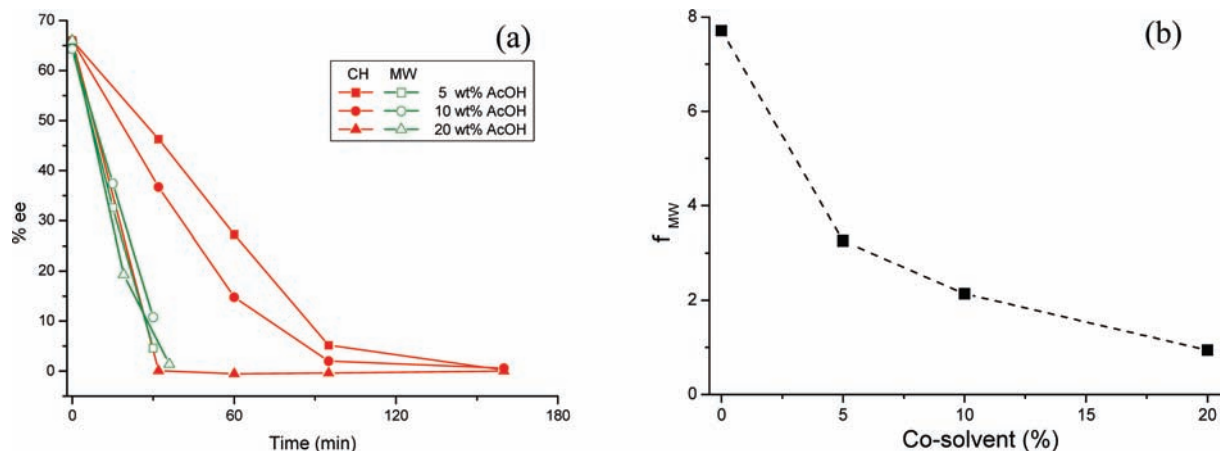


Figure 4. (a) Racemization of (*R*)-*N*-acetylindoline-2-carboxylic acid (66% ee) with addition of cosolvent (wt% acetic acid) at 130 °C for conventional (CH) and microwave heating (MW) conditions and (b) correlation of cosolvent addition with the microwave effect.

has been compared to the enantiomerically pure substrate and the racemic product. The spectrum shows another set of peaks, but no conclusive evidence can be produced from this analysis.

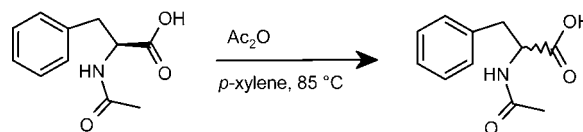
The increase of ee in time could, however, not be explained by the method of sampling, which was checked by comparing representative samples with the direct workup of the whole batch. An increase of % ee in a dynamic system during a longer period of days has also been demonstrated by Blackmond et al.¹⁰ The increase in ee is explained by a slight enantiomeric imbalance which directs the trend to a single chiral solid state.

The Influence of Temperature. The racemization of *N*-acetylindoline-2-carboxylic acid was also conducted below 130 °C to study the influence of temperatures. This resulted for this case in an incomplete racemization which is shown in Figure 1b. The influence of temperature on the racemization is elaborated in more detail in the section of “The Influence of Substrate”.

The Influence of Microwave Heating. An identical experimental setup and identical conditions were applied for both heating methods with proper stirring and internal temperature control by fiber optics, which enables a direct comparison between all experiments. All the heterogeneous reactions were accelerated by microwave heating (Figure 4).⁴ Additional heating experiments with microwave irradiation demonstrated that neither the solid, *N*-acetylindoline-2-carboxylic acid, nor the liquid increased in temperature, i.e. selective heating of both solid and liquid was not observed. Alternatively, experiments with homogeneous mixtures did not reveal any reaction rate enhancement by switching from conventional to microwave heating. In combination with the low energy of a microwave photon ($\sim 10^{-5}$ eV) a mechanistic change of racemization by microwaves is highly unlikely.

The reaction takes place in the phase boundary region of solid and liquid.⁴ The reactants and the intermediates in this phase boundary region selectively interact with microwaves due to their relatively polar character. Note that, the concentrations of reactants and intermediates in the phase boundary region differ from bulk. Local heating occurs, which simultaneously

Scheme 5. Racemization of *N*-acetylphenylalanine



increases both solubility and reaction rates. Bulk temperature, however, remains relatively low (and is identical to the temperature in the experiment where the reaction mixture was conventionally heated).

The Influence of Substrate. To understand the peculiar mechanistic phenomena observed in the racemization of *N*-acetylindoline-2-carboxylic acid and to gain more insight into the related microwave effect, another chiral *N*-acetyl amino acid was synthesized and racemized. One alternative substrate, in which formally the NH-Ph band was cleaved, was selected, e.g., *N*-acetylphenylalanine (see Scheme 5).

Under the benchmark conditions (130 °C), the racemization of (*S*)-*N*-acetylphenylalanine was completed within 5 min. For practical reasons, the temperature was lowered to 85 °C (Figure 5). As with *N*-acetylindoline-2-carboxylic acid, microwave heating increases also the reaction rates of the heterogeneous racemization of *N*-acetylphenylalanine. Under the studied reaction conditions, the microwave effect is relatively high at

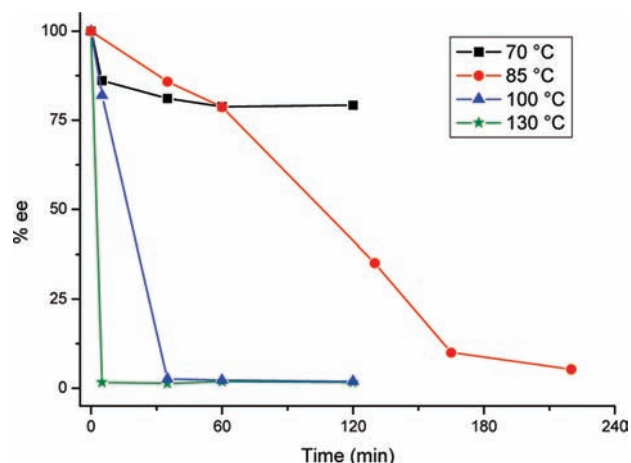


Figure 5. Racemization of (*S*)-*N*-acetylphenylalanine at various temperatures.

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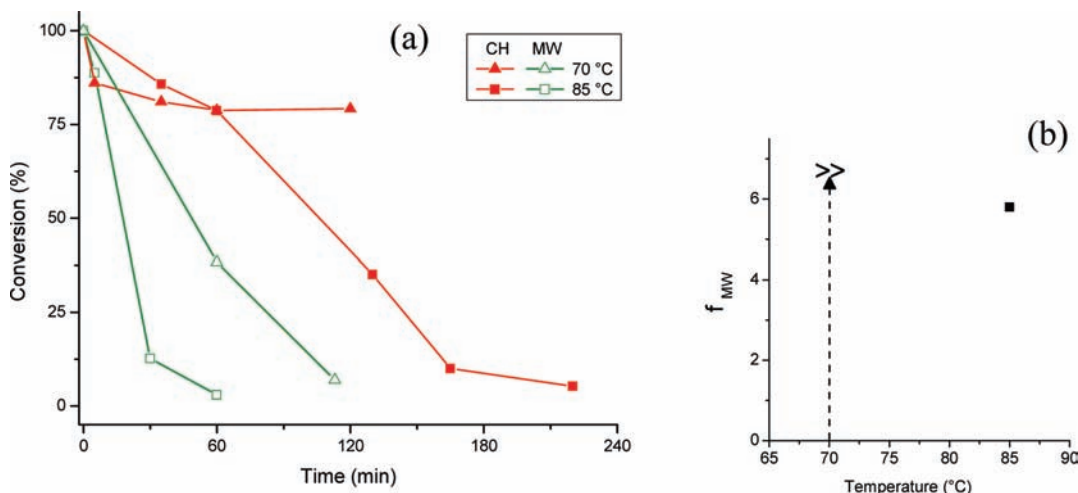


Figure 6. (a) Racemization of (*S*)-*N*-acetylphenylalanine at 70 °C and 85 °C for conventional (CH) and microwave heating (MW) and (b) influence of temperature on the microwave effect.

70 °C, based on the absence of full racemization under conventional heating (see Figure 6), and a factor of nearly six at 85 °C.

The heat of dissolution ($\Delta_s H^\ominus$) of *N*-acetylphenylalanine as the racemic mixture or in the enantiomerically pure form was calculated as approximately 85 kJ/mol (see eq 2). The solubility (S ; mol·L⁻¹) of the substrate has been measured at a series of temperatures (T). The large value of $\Delta_s H^\ominus$ indicates that heat or mass transfer (diffusion) is potentially rate-determining for the racemization, and therefore, these limitations are most likely to be located at the boundary layer of the solid particles.⁹ Racemization appears to be fast, and hence, measurements in the liquid phase show only the presence of a racemic mixture for all substrates.

The heat of dissolution ($\Delta_s H^\ominus$) for *N*-acetylindoline-2-carboxylic acid is 75 kJ/mol, also relatively high.¹¹

$$\ln\left(\frac{S(T_2)}{S(T_1)}\right) = -\frac{\Delta_s H^\ominus}{R} \left(\frac{1}{T_2} - \frac{1}{T_1}\right) \quad (2)$$

Transfer from Batch to Microwave-Heated Flow Processing

Only flow processing enables scaling up with the application of microwave heating, due to the limited penetration depth of microwaves. Most studies with continuous-flow reactors are

reported in the field of organic chemistry, applying conventional heating: so-called flow chemistry.¹³

Today's flow chemistry is based on the principle of Merrifield's solid-phase peptide synthesis.¹⁴ Solid-phase chemistry itself is specifically used under flow conditions,¹⁵ and this type of work has been extensively studied and promoted by, for example, Ley and Baxendale.¹⁶

Initial research into flow chemistry by microwave heating was done by Strauss and co-workers. The first publication of his work appeared in 1992 with positive expectations of this novel reactor design for the future.¹⁷ The combination of microwave heating and flow chemistry was also investigated by groups with expertise primarily in one of these enabling techniques.^{18–20} Attempts to scale up flow chemistry usually involve homogeneous systems or heterogeneous systems with immobilized reagents/catalysts.²¹ There is, to the best of the authors knowledge, only one small-scale example of an inorganic solid–liquid continuous flow system.²² Interestingly,

- (11) Solubility in *p*-xylene of (*S*)-*N*-acetylphenylalanine is 3.2, 4.1 and 27 mmol/L at 85, 100, and 115 °C; of (*R,S*)-*N*-acetylphenylalanine is 2.3, 5.4, and 21 mmol/L at 85, 100, and 115 °C and of (*R,S*)-*N*-acetylindoline-2-carboxylic acid is 4.1, 8.9, and 24.4 mmol/L at 102, 116, and 132 °C, respectively.
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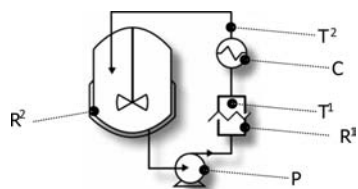


Figure 7. Batch-loop reactors for the racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid: R¹ = microwave-heated tubular reactor; R² = double-walled reactor vessel with overhead stirrer; P = (membrane-)pump; C = cooler with Archimedes screw; T¹ = temperature sensor inside the upper part of the tubular reactor and T² = temperature sensor just downstream the cooler.

Table 1. Racemization of *N*-acetylindoline-2-carboxylic acid under different reaction conditions (A and B) in continuous-flow reactor in batch-loop mode

entry	parameters	experiment A	experiment B
1	(<i>S</i>)- <i>N</i> -acetylindoline-2-carboxylic acid	178 g (<i>S</i>)	126 g (<i>S</i>)
2		0.87 mol	0.62 mol
3	<i>p</i> -xylene	679 g	650 g
4	acetic acid	<i>a</i>	72 g
5	acetic anhydride	22.3 g	14.8 g
6		0.22 mol	0.14 mol
7	wt % substrate	21	15
8	wt % cosolvent (acetic acid)	<i>a</i>	10
9	flow rate	216 mL·min ⁻¹	222 mL·min ⁻¹
10	total reaction time	263 min	182 min
11	interruption by:	plugging	plugging

^a = little water present, which will convert acetic anhydride into acetic acid (<2 wt %).

the majority (>75%)²³ of fine chemical processes involves heterogeneous reactions.

In general, reactions requiring short times for acceptable conversions (<30 min) can be performed continuously. However, for medium long reaction times (<3 h) typically a batch-loop mode is preferred (Figure 7).

Within the racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid, heterogeneity is governed by the solubility of the substrate. Changes in reaction conditions, such as temperature or the amount of cosolvent influence the performance of the batch-loop reactor. Also, fouling may be influenced. Two experiments under different conditions were conducted using (*S*)-*N*-acetylindoline-2-carboxylic acid as the substrate; see Table 1. Although each run was prematurely stopped due to plugging, a prediction based on sampling made a comparison with the performance of the stirred batch reactor possible. The main

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(24) After addition of acetic anhydride to the reaction mixture a fast decrease of the enantiomeric excess was observed in the small-scale batch experiments (a and b of Figure 8) in the first period (<60 min). During the microwave-heated experiment the racemization steadily continued, while during conventional heating inhibition was temporarily observed (see also Figure 2). After 120 min the racemization rate increased as the solubility of the substrate rose, see Figure 1. For the small-scale batch reaction conventional and microwave heating gave rise to different reaction rates. The flow experiment behaved similarly to the microwave-heated batch experiment as illustrated by the absence of an inhibition period after the addition of the catalyst. Reaction rates based on enantiomeric excess drop from 90 to 70% ee are shown in Table 2 for both the batch experiments and experiment A.

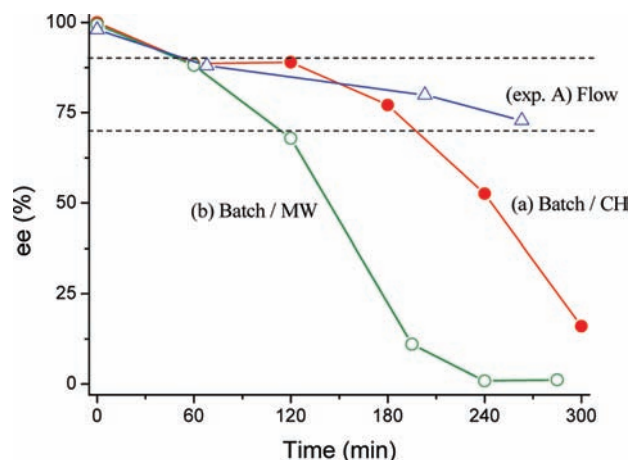


Figure 8. Racemization of experiment A in batch-loop mode compared to (a) conventional and (b) microwave-heated batch experiment under comparable conditions.

Table 2. Reaction rates (interval between 90 and 70% ee) of the racemization of *N*-acetylindoline-2-carboxylic acid under conventional and microwave heating conditions

entry	conditions	overall reaction rate [Δee·min ⁻¹]	fractional residence time ^a	corrected reaction rate [Δee·min ⁻¹]
1	batch (a); CH	-0.20	1	-0.20
2	batch (b); MW	-0.34	1	-0.34
3	experiment A	-0.08	0.21	-0.36

^a Fractional residence time in the reactor compared to the total reaction time [based on the ratio the volume of the microwave-heated tubular reactor (R¹, 180 mL) per total reaction volume (850 mL); overall rate = V_R¹/V_{tot}· rate (MW, R¹)]

difference between these two runs was the amount of cosolvent. In the first run, the racemization was performed without cosolvent. In the second run, acetic acid was added to decrease the heterogeneity, thereby reducing the risk of plugging.

Experiment A. In this experiment the racemization in *p*-xylene was performed without cosolvent.²⁴ The results are depicted in Figure 8 and Table 2.

Ideally, experiment A should have gone to completion to demonstrate that complete racemization can take place in the batch-loop reactor. However, plugging urged preliminary interruption of experiment A. Experience from earlier racemization experiments taught us that inhibition is only observed during the initial period, after which the reaction goes to completion.⁴ This observation, combined with the relative reaction rates, shows that the conversions in the batch-loop reactor closely resemble those of the microwave-heated small-scale batch

(25) After addition of acetic anhydride some technical problems occurred. The reaction mixture was temporarily collected in one vessel at a temperature below 20 °C. The system was restarted, and two large aliquots were taken to perform two experiments batchwise by oil-bath heating at 60 and 122 °C, see Figure 9. As a result of these large aliquots, the total reaction volume in the microwave-heated batch-loop system was less than that in experiment A. As a consequence the fractional residence time (= real reaction time) in tubular reactor R1 (Figure 7) is higher than in experiment A, see entries 3 and 4 in Table 3. Experiment B was executed at 127 °C in the batch-loop reactor. The temperature in vessel R2 (Figure 7) was below 60 °C (manually measured). The low reaction rate at 60 °C (Figure 9) allows to neglect racemization in vessel R2. Reaction rates based on an enantiomeric excess decrease from 86 to 34% ee (area between dotted lines in Figure 9) were compared between three batch experiments (c, d, e) and experiment B (Table 3).

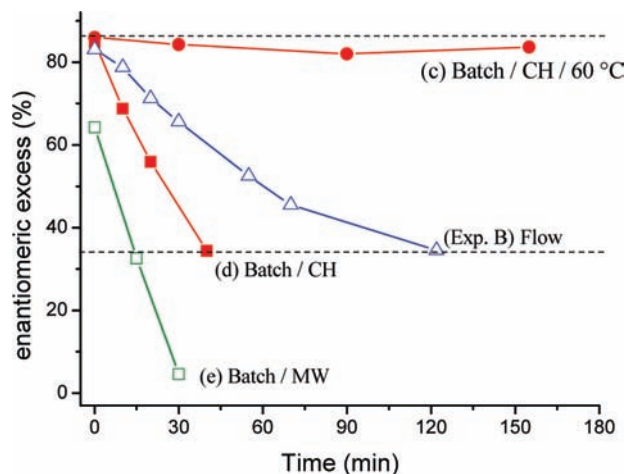


Figure 9. Racemization of experiment B in batch-loop mode compared to (c) conventionally heated at 60 °C, (d) conventionally heated at 122 °C, and (e) microwave-heated at 129 °C batch experiments under comparable conditions.

Table 3. Reaction rates (interval between 86 and 34% ee) of racemization of *N*-acetylindoline-2-carboxylic acid under different reaction conditions

entry	conditions	overall reaction rate [$\Delta ee \cdot \text{min}^{-1}$]	fractional residence time ^a	corrected reaction rate [$\Delta ee \cdot \text{min}^{-1}$]
1	batch (c); CH (60 °C)	-0.015	1	-0.015
2	batch (d); CH (122 °C)	-1.26	1	-1.26
3	batch (e); MW (129 °C) ^b	-2.05	1	-2.05
4	experiment B (127 °C)	-0.55	0.23	-2.43

^a Fractional residence time in the reactor compared to the total reaction time [based on the ratio the volume of the microwave-heated tubular reactor (R^1 , 180 mL) per total reaction volume^c (785 mL); overall rate = $V_R^1/V_{\text{tot}} \cdot \text{rate (MW, } R^1)$].
^b Reaction rate observed under microwave heating and comparable conditions. ^c $V_{\text{tot}} = V_{\text{premixed}} - V_{\text{sampling}}$; 785 mL = 850 mL - 65 mL.

experiment. In this case, racemization can in principle partially continue outside the tubular reactor, before a temperature is reached at which the rate of racemization is negligible. However, continuation of the racemization outside the microwave-heated tubular reactor R^1 appears to be insufficient to distinguish it from a measurement error.

Experiment B. In experiment B acetic acid was added to reduce the heterogeneity of the system.²⁵ The results are depicted in Figure 9 and Table 3.

Experiment B allows us to make a fair comparison between microwave and conventional heating for the racemization efficiency during a longer period (with respect to experiment A) on the basis of drops in the enantiomeric excess. Again the estimated conversion of the microwave-heated experiment proved to be in line with expectations.

The racemization was effective during a longer period and in a larger volume outside the microwave-heated tubular reactor R^1 , due to the deliberate absence of cooling power in cooler C (Figure 7) as compared to that in experiment A.

In summary, based on the experiments discussed in this section it can be concluded that the efficacy of the microwave effect described in the batch experiments has also been

demonstrated in the batch-loop reactor with respect to larger-scale applications.

Conclusions

For the homogeneous systems, reaction rate enhancements could not be detected when conventional heating was replaced by microwave irradiation. However, for heterogeneous mixtures different results were obtained. Here the rate-determining step appeared to be crucially influenced. During the racemization of two types of *N*-acetylamino acids (*N*-acetylindoline-2-carboxylic acid and *N*-acetylphenylalanine), significant microwave effects²⁶ were indeed observed under various conditions. Changing the degree of heterogeneity directly influenced the magnitude of the microwave effects. There is no doubt that there is a positive correlation between the heterogeneity of the system and the observed microwave effects. Presumably, the racemization of *N*-acetylamino acids under the applied reaction conditions occurs in the phase boundary region near the solid particles. Neither the (pure) solvent (*p*-xylene; loss tangent ≈ 0.0011)²⁷ nor the solid (*N*-acetylamino acid) absorb microwaves effectively. While the existence of hot-spots being unlikely to occur in this situation, selective heating of the interphase between solid and liquid is more plausible. Mechanistically nothing is altered, but the rate-limiting step is influenced indirectly by microwave heating. In agreement with the high heat of solution ($\Delta_s H^\ominus = 85 \text{ kJ/mol}$), small changes in temperature also have a larger effect on the solubility of the *N*-acetylamino acid.

In solution only a racemic mixture could be measured throughout the whole racemization process. The reaction occurs in the interphase and microwave energy directed to this layer, where the reaction takes place, can lead to a beneficial effect on the intrinsic reaction rates.

Experimental Section

In our commercially available setup, automated multimode microwave ovens were used, the MicroSynth and FlowSynth are from Milestone srl (Italy). These ovens operate at 2.45 GHz and are temperature controlled by means of a fiber-optic sensor (ATC-FO, fluoroptic probe inserted via a Teflon-coated ceramic well). During our microwave experiments the maximum power was set at 100 W. The average power input was 18 W (50 °C) and 76 W (100 °C). The reaction mixture was identified by ¹H NMR, GC-MS, and GC-FID, and conversion was determined by ¹H NMR. ¹H NMR spectra were recorded in CDCl₃ using a Varian Mercury 200 MHz with the aid of 1,3,5-tri-*tert*-butylbenzene as the internal standard. The proton chemical shifts were calibrated to tetramethylsilane (TMS).

Racemization of Wet (*R*)-*N*-Acetylindoline-2-carboxylic Acid of 66% ee (MW). A round-bottomed flask was charged with wet ($\sim 5 \text{ wt } \% \text{ H}_2\text{O}$) *N*-acetylindoline-2-carboxylic acid (1.78 g, 8.7 mmol, 66% ee *R*) and *p*-xylene (5.5 g). This mixture was heated in a Dean–Stark distillation setup to azeotropically remove water ($\sim 1.5 \text{ mL}$ distillate). The total mass of the

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(27) Magee, M. D.; Walker, S. *Trans. Faraday Soc.* **1966**, *62*, 1748.

reaction mixture was adjusted at 7.0 g with solvent, and the mixture was heated to 130 °C in the Milestone microwave oven. (A Weflon bar was added during MW heating at 0 wt % cosolvent.) Then, acetic anhydride (100 μL , 1.1 mmol) was added. After 2 h water (100 μL) was added, and via a Dean–Stark distillation setup *p*-xylene/water/acetic acid was distilled from the reaction mixture (~2.5 mL distillate). After cooling, the solid was filtered and washed twice with *p*-xylene (2 mL) and dried under reduced pressure at 50 °C. The reaction was monitored by quenching a sample (~50 mg) with water (25 μL) to neutralize the anhydride. The samples were generously dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL), and *n*-hexane (72 mL) and analyzed by HPLC on a chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v %), isopropanol (10 v %), and *n*-hexane (89 v %). The yield after workup was 1.35 g (76%). The same procedure was followed for the conventionally heated experiment by substituting microwave irradiation with oil-bath heating, except for the usage of a Weflon bar at 0 wt % cosolvent. Yield after workup: 1.62 g (91%).

Racemization of Dry (*S*)-*N*-Acetyldoline-2-carboxylic Acid of 99% ee (MW). A round-bottomed flask was charged with (*S*)-*N*-acetyldoline-2-carboxylic acid (1.78 g, 8.7 mmol, 99% ee (*S*)) and *p*-xylene (5.5 g). The mixture was heated to 130 °C in the Milestone microwave oven. (A Weflon bar was added during MW heating at 0 wt % cosolvent.) Then, acetic anhydride (100 μL , 1.1 mmol) was added. After 2 h water (100 μL) was added, and *p*-xylene/water/acetic acid was distilled from the reaction mixture. After cooling, the solid was filtered and washed twice with *p*-xylene (2 mL) and dried under reduced pressure at 50 °C. The reaction was monitored by quenching a sample (~50 mg) with water (25 μL) to neutralize the anhydride. The samples were generously dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL), and *n*-hexane (72 mL) and analyzed by HPLC on a chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v %), isopropanol (10 v %), and *n*-hexane (89 v %). The same procedure was executed for the conventionally heated experiment substituting microwave irradiation with oil-bath heating, except for the use of a Weflon bar at 0 wt % cosolvent.

Racemization of Dry (*S*)-*N*-Acetyldoline-2-carboxylic Acid of 99% ee (CFR). [Experiment A]. A round-bottomed flask was charged with dry (*S*)-*N*-acetyl indoline-2-carboxylic acid (178 g, 0.87 mol, 99% ee (*S*)) and *p*-xylene (679 g). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 216 mL·min⁻¹ and heated to 130 °C (*T*¹). Cooling was applied on top of the reactor. Subsequently, acetic anhydride (22.3 g, 0.22 mol) was added to the flask, and the set temperature was maintained for a period of 263 min. Total reaction volume was 850 mL. Average power usage during reaction was calculated to be 407 W. During the reaction, aliquots (~50 mg) were taken and quenched with water (25 μL) to neutralize the anhydride. The samples were

generously dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL), and *n*-hexane (72 mL) and analyzed by HPLC on a chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v %), isopropanol (10 v %), and *n*-hexane (89 v %).

[Experiment B]. A round-bottomed flask was charged with dry (*S*)-*N*-acetyldoline-2-carboxylic acid (126 g, 0.62 mol, 99% ee *S*) and *p*-xylene (650 g). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 222 mL·min⁻¹ and heated to 130 °C (*T*¹). No cooling was applied on top of reactor. Subsequently, acetic anhydride (14.8 g, 0.14 mol) was added to the flask, and the set temperature was maintained for a period of 182 min. The total reaction volume was 785 mL. The average power usage during reaction was calculated to be 280 W. During the reaction, aliquots (~50 mg) were taken and quenched with water (25 μL) to neutralize the anhydride. The samples were generously dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL), and *n*-hexane (72 mL) and analyzed by HPLC on a chiral column (Daicel, Chiracel OD) with an eluent consisting of formic acid (1 v %), isopropanol (10 v %), and *n*-hexane (89 v %).

***N*-Acetyl-(*S*)-phenylalanine.** A round-bottomed flask was charged with (*S*)-phenylalanine (19.8 g, 0.12 mol) and aqueous (30 mL) NaOH (4.8 g, 0.12 mol). To this mixture was added acetic anhydride (12.24 g, 0.12 mol) dropwise with the simultaneous addition of an aqueous solution (15 mL) of NaOH (4.8 g, 0.12 mol) under vigorous stirring and at room temperature. The temperature was kept below 30 °C, and pH was maintained at around 10. The addition procedure of acetic anhydride in combination with NaOH was repeated once after 30 min. This mixture was extracted with ethyl acetate (100 mL), the pH was set at 6 with 6 M HCl under vigorous stirring with cooling in an ice-bath. The extraction procedure was repeated for pH values set at 5, 4, and 3. The organic layers were combined and subsequently washed with brine (100 mL) and demi-water (50 mL). Organic solvent was removed under reduced pressure. The yield after workup was 21.0 g (84%). ¹H NMR (CD₃OD, 400 MHz) typical signals δ (ppm) 7.51 (m, 5H, Ar-*H*), 4.92 (m, 1H, CH-CH₂), 3.45 (dd, 1H, CH-CH₂), 3.20 (dd, 1H, CH-CH₂), 2.15 (s, 3H, CO-CH₃). Measured: $[\alpha]^{23}_{\text{D}} +29.7^\circ$ (*c* = 10, MeOH), literature²⁸ $[\alpha]^{23}_{\text{D}} +33^\circ$ (*c* = 10, MeOH).

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